Ulcerated nodules in a sporotrichoid distribution

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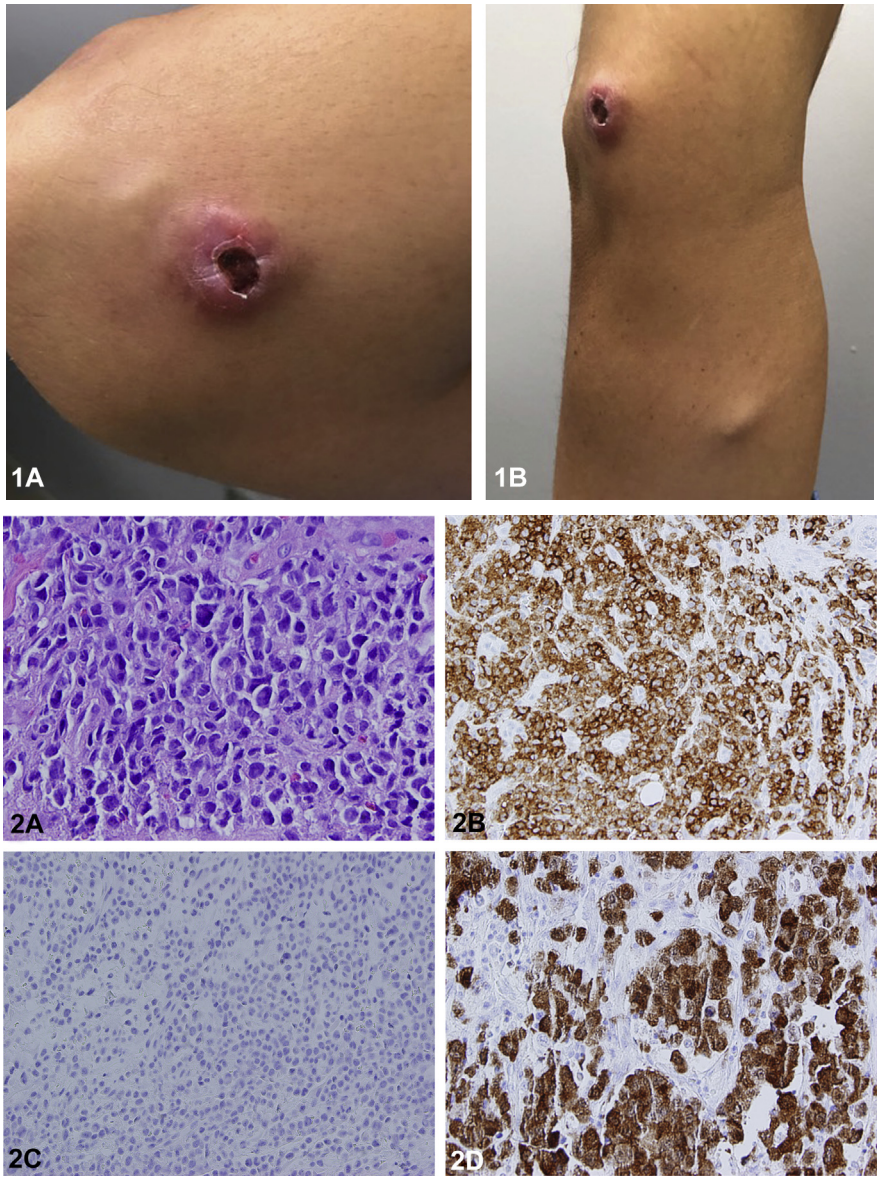

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A 42-year-old man presented with a 3-month history of persistent ulcerated nodules (Fig 1). History was relevant for deployment to the Middle East, Africa, Turkey, and South East Asia. He also reported skinning squirrels and butchering hogs on his farm in Missouri. Review of systems found intermittent fevers and night sweats. Prior treatment included multiple oral antibiotics without improvement. Examination found ulcerated, firm, pink nodules on the right forearm, elbow, and arm in sporotrichoid distribution without palpable lymphadenopathy. A punch biopsy was obtained and staining performed, including hematoxylin-eosin (Fig 2, *A*), CD30 (Fig 2, *B*), anaplastic lymphoma kinase (ALK-1) (Fig 2, *C*; control, Fig 2, *D*).

Question 1: What is your diagnosis?

A. *Bacillus anthracis*

B. Leishmaniasis

C. Lymphomatoid papulosis (LyP)

D. Primary cutaneous anaplastic large cell lymphoma (PC-ALCL)

E. Tularemia

Answers:

A. *Bacillus anthracis* — Incorrect. *B anthracis* is a spore-forming, toxin-producing bacteria found in soil. Risk factors for cutaneous anthrax include living in Turkey (endemic area) and butchering meat (mainly cows, also reported in pigs). However, ulcerations rapidly progress to eschars, and a $CD30^+$ infiltrate would not be observed. Gram stain would find spore-forming rods.

B. Leishmaniasis — Incorrect. Infection with *Leishmania* results in a papule or nodule with central ulceration at the site of a sandfly bite. Although the patient has risk factors for exposure to Old World leishmaniasis, geographically distributed from West Africa to Central Asia, histopathology would show *Leishmania* amastigotes within histiocyte cytoplasm.[1]

C. LyP — Incorrect. LyP presents as recurrent crops of small papulonodules. Although LyP is on the spectrum of $CD30^+$ lymphoproliferative disorders, lesions classically resolve and reoccur over weeks to months. Histopathology for type A LyP reveals a wedge-shaped dermal infiltrate of $CD30^+$ lymphoid cells with numerous neutrophils and eosinophils.[2]

D. PC-ALCL — Correct. PC-ALCL presents as a solitary tumor or several grouped papules/-nodules. Histopathology shows diffuse dermal infiltration of $CD30^+$/ALK-1^- atypical mononuclear cells with hyperchromatic horseshoe-shaped nuclei, numerous mitoses, and apoptotic bodies.[2]

E. Tularemia — Incorrect. Tularemia is caused by the gram-negative coccobacillus *Francisella tularensis*. Although rabbits most commonly transmit tularemia, squirrels can also be infected. The ulceroglandular form presents with a papule that progresses to an ulcer with eschar formation. Histopathology shows suppurative granulomatous inflammation and would not show a $CD30^+$ lymphoid infiltrate.

Question 2: Which of the following immunohistochemical markers would indicate that the diagnosis is likely systemic rather than primary cutaneous?

A. Negative CD56

B. Negative epithelial membrane antigen (EMA)

C. Positive ALK-1

D. Positive B-cell lymphoma 2 (Bcl-2)

E. Positive cutaneous lymphocyte antigen (CLA)

Answers:

A. Negative CD56 — Incorrect. CD56 is expressed in 12% to 75% of PC-ALCL and is positive in systemic ALCL and therefore does not help differentiate between these 2 entities.[2]

B. Negative EMA — Incorrect. EMA is typically negative in PC-ALCL and positive in systemic ALCL.[2]

C. Positive ALK-1 — Correct. Positive ALK-1 would indicate that the ALCL is more likely systemic, as the t(2;5) gene rearrangement involving the ALK gene is an extremely rare event in PC-ALCL compared with nearly 60% of all systemic ALCL. ALK-1 can help differentiate the 2 entities in indeterminate cases.[2]

D. Positive Bcl-2 — Incorrect. Bcl-2 does not help differentiate between these 2 entities, as it is positive in 30% of PC-ALCL and is positive in systemic ALCL.[2]

E. Positive CLA — Incorrect. Most cases of PC-ALCL express CLA, whereas CLA is negative in systemic ALCL.[2]

Question 3: Which of the following medications is US Food and Drug Administration (FDA)-approved for the treatment of this condition?

A. Bexarotene gel

B. Brentuximab vedotin (BV)

C. Imiquimod

D. Interferon

E. Methotrexate

Answers:

A. Bexarotene gel — Incorrect. Bexarotene is FDA approved for the topical treatment of cutaneous lesions in patients with cutaneous T-cell lymphoma, stage 1A and 1B, who have refractory or persistent disease after other therapies or who have not tolerated other therapies. Data regarding the use of topical bexarotene gel are limited to case reports and the control arm of the ALCANZA trial in which the response rate was low.[3]

B. BV — Correct. BV is an anti-CD30 monoclonal antibody that is FDA approved for the treatment of adult patients with PC-ALCL who have received at least 1 prior systemic therapy.[4] Approval was based on a phase 3, randomized clinical trial (ALCANZA), which randomized patients to receive BV or either methotrexate or bexarotene. BV resulted in complete resolution of skin involvement in 10 of 16 patients (63%) with PC-ALCL.[3]

C. Imiquimod — Incorrect. The use of topical imiquimod has been described in case reports and case series; however, it is not FDA approved for PC-ALCL.[5]

D. Interferon — Incorrect. Interferon is not FDA approved for PC-ALCL, and because of its toxicity, it is generally reserved for patients who progress on or who are intolerant to methotrexate or bexarotene.

E. Methotrexate — Incorrect. Methotrexate is not FDA approved for PC-ALCL. However, low-dose (less than 25 mg/wk) is considered first-line therapy for multifocal PC-ALCL when radiotherapy is not feasible.[2]

Patient Course: The patient underwent local radiation to the right arm, which he tolerated well, but new lesions developed proximal to the radiated port. Thus, he was started on brentuximab for 4 cycles and experienced complete remission.

Abbreviations used:

ALCL: anaplastic large cell lymphoma
ALK: anaplastic lymphoma kinase
Bcl-2: B-cell lymphoma 2
BV: brentuximab vedotin
CLA: cutaneous lymphocyte antigen
EMA: epithelial membrane antigen
FDA: US Food and Drug Administration
PC-ALCL: primary cutaneous anaplastic large cell lymphoma

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